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# The Role of Activity in Development of the Visual System

Review

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**Neuronal activity is important for both the initial formation and the subsequent refinement of anatomical and physiological features of the mammalian visual system. Here we examine recent evidence concerning the role that spontaneous activity plays in axonal segregation, both of retinogeniculate afferents into eye-specific layers and of geniculocortical afferents into ocular dominance bands. We also assess the role of activity in the generation and plasticity of orientation selectivity in the primary visual cortex. Finally, we review recent challenges to textbook views on how inputs representing the two eyes interact during the critical period of visual cortical plasticity.**

## Introduction

One of the oldest and most controversial questions in modern biology is encompassed by the nature versus nurture debate: to what extent are living structures and functions determined by intrinsic factors such as genetic disposition, and to what extent can they be influenced and shaped by the environment? Perhaps the most studied part of the brain in that respect is the mammalian visual system. In this selective review we shall highlight recent evidence concerning the role of neuronal activity during the development of the visual system. In the first part, we shall examine intrinsic processes that are independent of visual experience; the second part addresses mechanisms by which the environment, that is visual experience, affects visual system development. Experience-independent and experience-dependent processes roughly correspond to two stages of development: the initial formation of anatomical and physiological maps and the subsequent maturation or refinement, respectively, of these maps to produce a mature visual system. We shall pay particular attention to the role that neuronal activity plays during both these stages.

Examples of intrinsic, experience-independent processes include the formation of layers in the lateral geniculate nucleus (LGN) and of ocular dominance bands in layer 4 of the primary visual cortex (V1). Although these features form prior to the onset of visually evoked activity, they could require spontaneously generated activity. For example, segregation of retinogeniculate axons was originally believed to be achieved by axon guidance and/or target recognition molecules, occurring independently of activity. Evidence over the last decade, however, has suggested that intrinsically generated activity might instruct or permit the establishment of crude maps on which subsequent experience-dependent refinements can be made [1]. Interestingly, early spontaneous activity has been observed in the retina (as well as in LGN and V1) with spatial patterns that resemble those seen later on in response to natural visual stimuli. These patterns of activity might be critical in shaping early connectivity in the visual system. In the first part of this review we shall examine recent evidence from several laboratories that has cast new light on the roles of guidance or recognition cues *versus* patterns of spontaneous activity in the development of visual thalamus and visual cortex.

While the requirement for (intrinsic) activity for initial pattern formation remains controversial, it is clear that visually driven activity is crucial for modifying the crude initial connectivity patterns into a mature, functioning network. This is true in particular for two of the most prominent characteristics of neurons in the primary visual cortex: orientation selectivity and binocularity. However, two main unresolved questions surround the mechanisms by which patterned activity during the sensitive period changes the receptive field properties of neurons in V1. First, does activity play an *instructive* or a *selective* role in shaping neuronal responses (see Box 1)? And second, how do channels carrying different activity patterns, such as the inputs from the two eyes, interact?

The traditional viewpoint on the nature of the interaction between the two eyes is that they compete for synaptic space; however, this has been challenged by new evidence from several sources. It is important to describe precisely what is meant by 'competition', as

### Box 1. Defining roles of activity

As with every scientific field, visual system development is plagued with jargon that will have little meaning to researchers not active in the field. Consequently we begin with definitions of several key terms that have become associated with different concepts regarding the role of activity in the development of the visual system.

***Instructive*** — Activity, be it spontaneous or stimulus-driven, is said to be instructive when it is necessary to establish or modify a neuronal structure or functional property, and when activity levels or patterns are directly related to the shape that this structure or function takes.

***Permissive*** — Activity is permissive if a certain threshold level is sufficient for normal development of a structure or function, but further increases in activity do not make a difference.

***Selective*** — Activity is selective when its presence is necessary to maintain a particular structure or response and its absence causes a degeneration or passive loss of responsiveness.

These terms are largely descriptive and, while useful for contrasting different concepts of development or comparing different features of the visual system, they seldom provide insight into the underlying mechanisms of visual system development.

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on its own, competition has little implication for mechanism. Hubel and Wiesel first described ocular dominance plasticity as being competitive when they noticed that binocular deprivation had a much milder effect on the ocular dominance of visual cortical neurons than monocular deprivation. It was not until the late 1980s, however, that Guillery formally defined the term ‘competition’; this definition has become widely accepted in the field and, as a result, has been adopted for common textbook use. Hence, this is the definition we use in this review, although we are aware that other researchers may define competition differently, especially in other systems. According to Guillery [2], competition is “an interaction between nerve cells or neuronal processes that all require the same resource in a developmental situation where a limited supply of this resource is available”. Guillery [2] went on to state that an interaction between two sets of inputs is competitive if in normal development “a weakening of one, generally by its destruction or deprivation, leads to an increased growth (or strengthening) of the other”.

During visual system development, inputs from the two eyes overlap in the LGN before segregating into eye-specific layers. Furthermore, while inputs from the two eyes may not overlap in layer 4 of the visual cortex before segregating into ocular dominance bands (see below), it is clear that the relative cortical territory devoted to these inputs can be dramatically altered by visual experience. We define these types of between-cell interaction as *heterocellular*. Similarly, during development, inputs from the two eyes may converge on the same neuron in the cortex, and the relative influence of the two eyes can be altered without large changes in the synaptic territory devoted to each eye.

These interactions can be either *heterosynaptic* — between synapses or groups of synapses — or *homosynaptic* — at one synapse or one group of synapses — and they are further subdivided by the direction (positive or negative) of the change. For example, Hebb’s postulate that increases in synaptic efficacy result when strong presynaptic activity is paired with strong postsynaptic activity is an example of homosynaptic long-term potentiation (LTP) [3]. In V1, monocular deprivation not only results in strengthening of the non-deprived eye synapses, but also in weakening of the deprived eye synapses. This form of long-term depression (LTD) could result from heterosynaptic or homosynaptic mechanisms. We shall review recent studies which indicate that homosynaptic, associative mechanisms are crucial for plasticity in response, not only to monocular deprivation, but to various paradigms of altered visual experience.

## Time Line of Development of the Visual System

Most of the studies reviewed here have been performed in the visual system of carnivores, specifically cats and ferrets. We therefore start with a brief overview of the key stages in the visual development of these species with respect to the nature of neural activity (Figure 1). In principle, however, similar stages of development are likely to be found in other species, including rodents and primates.

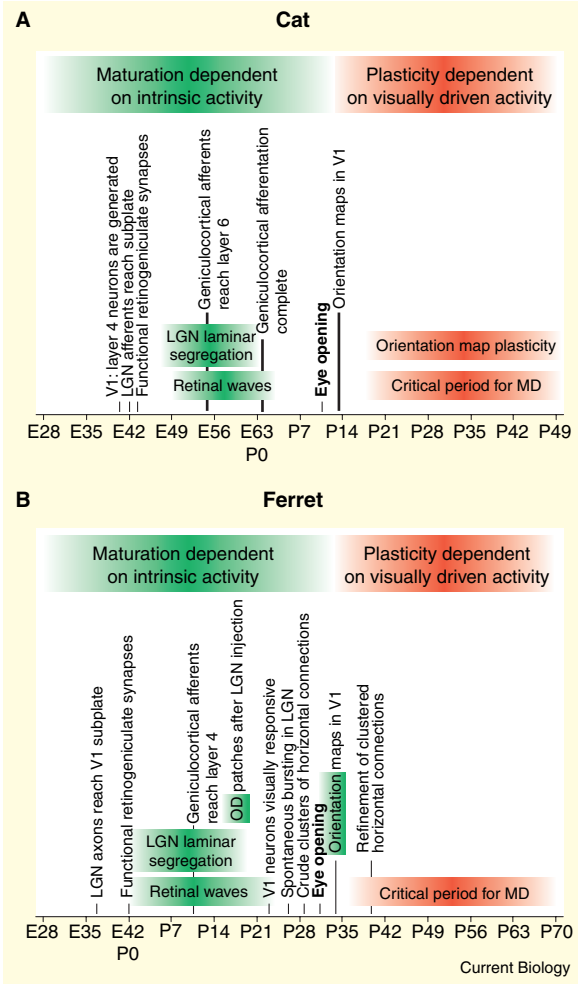


Figure 1. Timeline of development of the visual system in (A) cats and (B) ferrets.

Major events are plotted against embryonic (E) and postnatal (P) age. At birth, the development of the ferret lags that of the cat by about 3 weeks. In both species, maturation that is largely dependent on intrinsic activity is completed by the time of eye-opening, while plasticity dependent on visually driven activity sets on shortly afterwards.

Embryonic and early postnatal development in cats and ferrets occur largely in parallel, although with gestation periods of 9 weeks and 6 weeks, respectively, ferrets are born much more immaturely than cats, making them ideal subjects for investigating the very early stages of development. In both cats and ferrets, anatomical and physiological maturation of the retina precedes that of the LGN, which in turn precedes that of the primary visual cortex [4,5]. It is therefore tempting to hypothesize that the maturation of the LGN depends on retinogeniculate afferent activity, and similarly, that the early development of V1 is directed by activity in the geniculocortical afferents. Irrespective of whether or not activity plays a role in them, experience-independent processes are largely complete by the time of eye-opening, while experience-dependent processes set in very shortly after eye-opening.

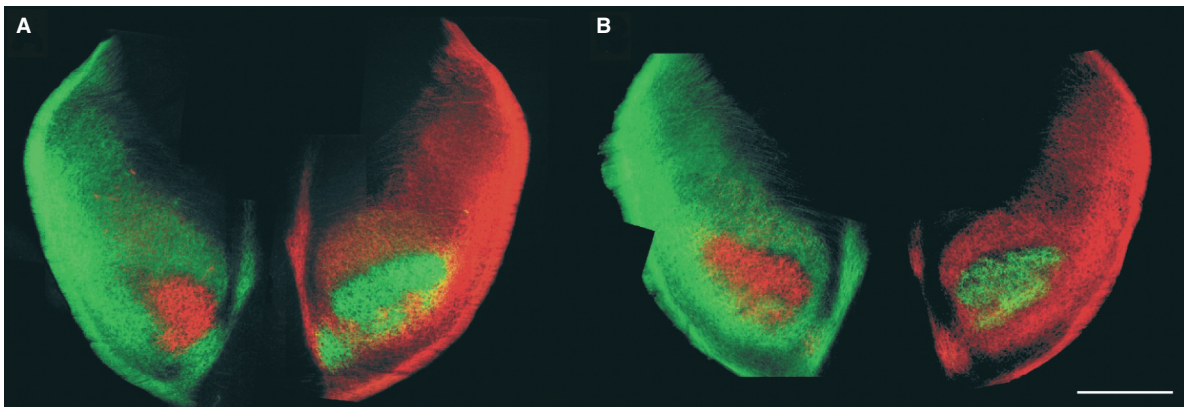


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Figure 2. Dependence of the size of the retinogeniculate projection on the relative strength of retinal-wave activity in the two eyes.

Micrographs show horizontal sections through the thalamus of two P10 ferrets (anterior, top; posterior, bottom). From P0 to P10, the left eye of the animal shown in (A) was injected with CPT-cAMP, a nonhydrolysable, membrane-permeable analogue of cAMP, which elevates intraocular cAMP levels, thereby inducing increased retinal wave activity. The left retina was labelled with FITC-conjugated cholera toxin B chain (CtB; green). The untreated right retina was labelled with TRITC-conjugated CtB (red). The only areas of overlap (yellow) are near the optic tract and are due to fibers of passage. Note that projections to layers A and A1 are completely segregated from each other; the projection from the treated eye is expanded at the expense of that from the untreated eye. The ferret shown in (B) received monocular saline injections from P1–P10, and both eyes were then injected with fluorescent CtB. Scale bar = 500 μm.

## Intrinsic Mechanisms in Visual System Development

### *The Role of Retinal Waves in Lamination of the LGN*

In very young ferret kits — from the day of birth to 21–25 days of age — waves of correlated activity periodically sweep across parts of the retina at a rate of once every minute or two [4,6]. In contrast to 'normal' visually evoked activity, retinal waves occur independently in the two eyes. So while the firing of neighbouring retinal ganglion cells is well correlated, firing of cells in corresponding locations in the two retinae is uncorrelated. Because of the partial decussation of the optic nerves at the chiasm, these corresponding locations map onto the same site in one of the two LGNs. Afferents representing the two eyes in the LGN are initially completely intermingled, but they segregate into characteristic left-eye and right-eye laminae at the time of the retinal wave activity [7]. It has therefore been suggested that within-eye correlated retinogeniculate activity, together with a lack of temporal correlation between the two eyes' inputs, causes lamination of the LGN [8], a process captured by the phrase "cells that fire together wire together".

A number of experiments have been performed to test this hypothesis. When activity in the LGN itself is blocked, by intracranial injection of tetrodotoxin, lamination of the LGN is disrupted [9,10] (but see [11], discussed below). Similarly, silencing retinal ganglion cells in only one eye results in the loss of much of that eye's territory in the LGN [12]. Moreover, in mutant mice lacking the β2 subunit of the nicotinic acetylcholine receptor, which lack retinal waves, retinogeniculate fibres do not segregate [13]. However, these studies relied on removal of activity and could therefore only prove that retinal activity is necessary for LGN lamination, not whether there is heterocellular, activity-based competition. An alternative explanation might be that a minimum level of activity is merely permissive, enabling retinal afferents to follow as yet unidentified guidance cues.

A direct test of the hypothesis that retinal waves instruct LGN lamination must involve manipulation of either the relative amounts or the temporal pattern of inputs from the two eyes. Stellwagen and Shatz [14] elevated intracellular levels of cAMP in ferret retinal ganglion cells by intraocular injections of forskolin, cholera toxin or a non-hydrolysable analogue of cAMP, thereby inducing increased retinal wave activity in the injected eye by about 40%. When only one eye had been injected, that eye's ipsilateral projection expanded to nearly twice its normal size (Figure 2). The increase of the contralateral projection, which normally already occupies about 88% of the LGN, was only modest. When, in contrast, both eyes were injected, increasing retinal wave activity binocularly, then territories in the LGN occupied by the two sets of afferents were indistinguishable from normal. These results strongly suggest that relative, rather than absolute levels, of activity in the two eyes determine the balance between the territories devoted to each eye in a competition-based manner [14]. In other words, activity plays an instructive, rather than a permissive, role in the development of the LGN.

It should be noted that Cook *et al.* [11] reported that silencing both retinae with tetrodotoxin does not prevent the segregation of retinogeniculate fibres, but delays it by approximately one week and prevents normal maturation of inhibitory circuits. This finding is very difficult to reconcile with those of Shatz and colleagues [9,10,14], but it is in good agreement with evidence from other systems, specifically the development of thalamocortical projections. Geniculocortical

afferents appear to segregate normally in layer 4 of ferret V1 in the absence of eyes [15] (see below). In rodent somatosensory cortex, blockade of cortical activity, either with tetrodotoxin or NMDA receptor antagonists, fails to prevent the segregation of geniculocortical axons ([16,17], reviewed in [18]). Similarly, NMDA receptor blockade in the thalamus does not prevent the formation of LGN layers [19], but does prevent the formation of 'on' and 'off' sublaminae [20].

### *The Role of Activity in the Development of Ocular Dominance Bands*

Perhaps the best-known paradigm for examining mechanisms of visual cortical development and plasticity is the segregation of geniculocortical afferents into ocular dominance (OD) bands in layer 4 of the primary visual cortex. These anatomical units correspond well with the physiological response properties of cortical neurons in columns throughout the thickness of the visual cortex. Pioneering physiological and anatomical studies of OD development and plasticity culminated in two textbook axioms: first, that geniculocortical terminals representing the two eyes are initially intermingled and segregate into OD patterns under the influence of retinal activity, either visually driven or spontaneous; and second, that afferents representing the two eyes compete for synaptic space in layer 4 based on relative levels of evoked activity.

Both of these views have been challenged recently. The first is discussed in this section, as recent evidence clearly indicates that segregation develops independently of retinal activity. The second is discussed in the following sections, as it is clear that the developmental plasticity of OD bands is dependent on visually driven activity.

The postnatal development of OD columns was first demonstrated by means of intraocular injections of radioactively labelled tracers [21], which are transported transneuronally via the LGN to the primary visual cortex. Terminal label was shown to be largely uniform in kittens at the time of eye-opening, with an adult-like OD pattern beginning to develop at the start of the fourth postnatal week [21]. In agreement with the hypothesis that incoming activity is crucial for normal afferent segregation [22], silencing retinal activity by repeated binocular tetrodotoxin injections prevents OD column formation [23].

Such input activity need not, however, be the result of visual stimulation, as studies of neonate macaque monkeys have shown [24]. Animals, which were delivered one week pre-term in the dark and had received a monocular injection of a radioactive tracer, exhibited normal, albeit somewhat weaker OD patterns, after having been kept in complete darkness for a week. Similarly, both optical imaging studies [25] and more recent anterograde as well as retrograde anatomical labelling studies [26] show that the onset of OD column formation in the cat is in the second postnatal week, where the optics at best permit only crude retinal images [27]. These results already suggest that visual experience is not necessary for OD segregation and that the mechanisms for OD column formation may be partially distinct from those mediating plasticity later in life [26]. But the possibility remained that spontaneous retinal activity, such as retinal waves, mediates the segregation of geniculocortical terminals.

Recent studies by Crowley and Katz [15,28], however, clearly show that retinal waves are unlikely to play a major role in OD band formation, as OD bands develop in the absence of any retinal input [15]. Furthermore, OD band formation may not be influenced at all by the balance of inputs from the two eyes [28]. In their first experiment [15], ferrets were binocularly enucleated between the day of birth and postnatal day (P) 18, before the ingrowth of geniculate axons into layer 4 of V1, and the pattern of geniculocortical projections was visualized after P70. Anterograde tracing following LGN injections of biotinylated dextran amine, and retrograde labelling by pressure injection of fluorescent microspheres into V1, both revealed patchy patterns of the same periodicity as in normal control animals [15]. Moreover, in normal ferret kits that received tracer injections confined to individual LGN layers, segregated patches of geniculocortical axons in layer 4 were seen as early as P16 to P18, less than a week after innervation of layer 4.

Crowley and Katz [28] found that severely changing the balance between retinal inputs by monocular enucleation between P7 and P14 had no significant effect on the widths of columns representing the deprived and non-deprived eyes, respectively. These data suggest a role for molecular cues in the formation of OD bands in layer 4, although it is still possible that patchy, patterned spontaneous activity, which is present in ferret V1 before eye-opening ([29], see below), or activity in the LGN, might drive afferent segregation in layer 4.

The question remains, why did the original studies using eye injections of $^{3}$H proline not show geniculocortical segregation. One likely possibility concerns the high solubility of $^{3}$H proline and the nature of the extracellular matrix in early postnatal brains. As development proceeds, the initially hyaluronan-rich, highly soluble matrix turns into a hyaluronan-sparse, highly insoluble matrix [30]. Hence any spillover of proline between synapses, either in the LGN or the cortex, will likely diffuse a much further distance in young, compared to old, animals. Whatever the explanation, it is clear that patterns of neural activity, originating in the retina, are not necessary for OD band formation.

### *The Role of Intrinsic Activity in the Development of Orientation Selectivity*

Despite the apparent lack of a role of retinal activity in OD band formation, it might yet play a part in the generation of cortical orientation selectivity. It is tempting to speculate that the waves of correlated neuronal activity that are observed in the retina prior to any visual experience are propagated first to the LGN and then on to V1. If this were the case, it could help to explain why, at eye-opening, a proportion of cells in V1 show the orientation selectivity and binocular responsiveness that are typical of the more mature visual cortex following normal visual experience. While early electrophysiological studies vary widely in quantitative terms, it appears that about a quarter of

recorded neurons in neonatal kitten cortex have some orientation selectivity, and that orientation preferences tend to be clustered around the cardinal horizontal and vertical axes [31,32].

These results have recently been confirmed and extended by functional imaging studies. While recording of single neurons in the visual cortex of very young animals is notoriously difficult and the low yield in cell numbers makes statistical significance hard to obtain, optical imaging of intrinsic signals allows repeated, unbiased recordings from a large area throughout visual cortical development. Optical imaging of the visual cortex of kittens that had been deprived of patterned vision from birth, by binocular lid-suture, revealed orientation preference maps of normal layout, albeit with a stronger contralateral-eye bias [25,33]. Interestingly, in young ferrets, orientation selectivity is much stronger when the animals are dark-reared beyond the time of eye-opening than when their eyes are kept shut by lid-suture [34], although prolonged dark-rearing causes a progressive deterioration of orientation maps.

This finding lends support to the notion that dark-rearing, to some extent, merely arrests visual cortical development, while the abnormal diffuse stimulation experienced through closed eye-lids has a deleterious effect (although some visual responses have been reported in V1 of binocularly deprived kittens [35]). However, it has recently been shown that, in the visual cortex of very young ferret kits, orientation-selective responses can be recorded through closed eye-lids up to two weeks prior to natural eye-opening [36]. This is precisely the period during which orientation selectivity displays seemingly passive maturation, regardless of rearing conditions [34]. These findings suggest that the development of orientation selectivity prior to eye-opening might result from patterned visual input. It also raises an important question — what happens rather abruptly around the time of natural eye-opening to make weakly correlated activity change from being beneficial to being disruptive to cortical development?

It has been shown that retinal waves are relayed to the developing LGN, driving trains of activity *in vitro* [37]. So is there any evidence that activity in the LGN caused by correlated waves of input from the retina is responsible for the early, experience-independent appearance of orientation selectivity in the visual cortex? Two papers by Weliky and Katz [38,39] suggest that this is likely to be the case. In the first paper [38], it is shown that synchronous bursts of spontaneous activity occur in the LGN of ferrets before eye-opening. The frequency of these bursts is similar to that of retinal waves, but significant correlation of activity between left-eye and right-eye layers is caused by cortical feedback.

In the second paper [39], disruption of the natural input patterns is reported to result in a degradation of early cortical orientation selectivity. Weliky and Katz [39] 'overrode' the spontaneous retinogeniculate drive with synchronous electrical burst stimulation by means of a fine wire cuff placed around one of the optic nerves, the other eye being enucleated. They found that, although the layout of orientation preference maps in the visual cortex appeared to be normal, orientation selectivity was lower at both the population and single-cell level. This argues in favour of an instructive role (see Box 1) of afferent activity in the development of neuronal response properties. Unfortunately, this result is somewhat ambiguous, as it is impossible to know whether the remaining orientation selectivity is intrinsic to the cortical network as a 'self-organizing' system [40] or whether it has been instructed by geniculate inputs despite the experimental manipulation.

Interestingly, synchronous bursts of spontaneous activity have recently been observed in multi-electrode recordings from awake ferret visual cortex prior to eye-opening [29]. Sites with precisely correlated activity were not uniformly distributed, but showed a patchy organization, with patches separated by about a millimetre. This organization is reminiscent of the network of clustered horizontal connections that begins to develop at the same time [41,42]. Long-range correlated activity was found to persist in the absence of geniculate input following optic nerve transection [29]. Clearly, spontaneous activity in the visual cortex is at least to some extent independent of geniculate input and may play a role in both the generation of orientation selectivity and the formation of ocular dominance columns (see above).

## Visually Driven Activity and Visual System Development

### *Instructive versus Selective Role of Experience in Orientation Selectivity*

One of the classical paradigms for studying whether activity plays a selective or an instructive role in shaping cortical responses is 'stripe-rearing' — rearing in an environment where only a single orientation is present. In this situation, a selective role for activity would imply that, from a starting point where roughly equal numbers of neurons respond to all possible orientations, only those receiving adequate stimulation from the environment will survive and mature, while others will lose responsiveness and may eventually degenerate. An instructive role for activity would mean that previously non-selective cells acquire a preference for the orientation present in the environment, or that cells shift their orientation preference towards the experienced orientation, while maintaining normal responsiveness.

In the 1970s, several groups addressed this issue using single-unit recording and a variety of rearing techniques. Doubts over the suitability of some of the rearing methods to limit orientation exposure, as well as over the potential for sampling bias inherent in recording a small number of cells from a cortical sheet of fairly regular architecture, meant that firm conclusions were difficult to draw [43].

We reared kittens in striped cylinders providing a single-orientation environment [44], and used optical imaging to assess quantitatively how much cortical territory was devoted to the experienced and other orientations, and how tightly tuned and how strong responses were [45]. We found that, in all animals

tested, the representation of the experienced orientation occupied a larger part of the cortical surface than other orientations. But orientations never seen by the animals still occupied significant portions of the visual cortex, arguing in favour of an experience-independent determination of cortical orientation preference.

Notably, we found that cells responding best to the experienced orientations, and those preferring other orientations, all exhibited a similar sharpness of tuning, and the overall responsiveness did not vary across the cortical surface. Specifically, it was not lower in regions responding best to non-experienced orientations than in those tuned to the orientation present in the environment. Together, these results demonstrated that visual experience plays an instructive role, whereby neurons shift their orientation preference towards the experienced orientation [45].

### *The Role of Activity in Ocular Dominance Plasticity*

Wiesel and Hubel first proposed the widely held viewpoint that ocular dominance plasticity reflects 'competitive' interactions between the two eyes for synaptic space. Competition-based theories arose from the finding that binocular deprivation was far less detrimental to the response properties, in particular binocularity, of neurons in area 17, than a similar period of monocular deprivation. More recent evidence suggests that the limiting factor for which afferents from the two eyes compete may be a retrogradely active molecule secreted by cortical neurons, such as a neurotrophin [46,47]. According to this view, active geniculate neurons can compete more efficiently than less active neurons. Hence, during monocular deprivation, the open eye is thought to out-compete the closed eye for the limiting factor and to induce synaptic weakening in the deprived-eye synapses.

The belief that geniculocortical afferents compete for synaptic space was largely based on studies where long periods of monocular deprivation were employed and large changes in afferent morphology were observed. In an important set of studies by Stryker and colleagues [48–50], however, it became clear that changes in afferent morphology and synapse densities are apparent days after the cortex becomes dominated by the non-deprived eye physiologically [51]. Therefore, the physiological shifts in ocular dominance observed following short periods of monocular deprivation must involve interactions between synapses upon single neurons.

Competition-based models of synaptic plasticity [40,52–54] generally invoke a heterosynaptic learning rule to explain interactions between two sets of inputs from different sources, in this case the two eyes. An alternative, the Bienenstock-Cooper-Munro (BCM) model [55], invokes a homosynaptic learning rule. The BCM model extends Hebb's postulate [56] by making synaptic change bidirectional — synapses can undergo homosynaptic LTD in addition to homosynaptic LTP. Furthermore, the direction or sign of the change in efficacy depends on a cell-wide, not synapse-specific, modification threshold that changes during development depending on the average firing rate of the postsynaptic cell. By invoking a sliding modification threshold, the time-averaged total synaptic weight need not remain constant, a requirement of most models based on heterosynaptic learning rules.

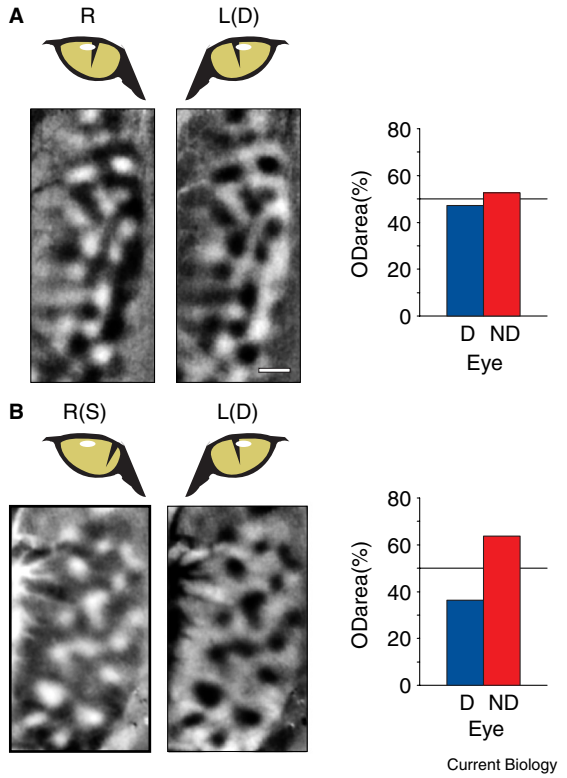


Figure 3. Recovery from monocular deprivation with and without correlated binocular input.

The images show OD maps recorded from V1 of the left hemisphere, ipsilateral to the previously deprived eye, of two littermate kittens which had the left eye sutured from P35–P45 (anterior, top; posterior, bottom). The animal depicted in (A) had 1.5 months of concordant binocular vision following re-opening of the deprived eye. The left activity map shows areas dominated by the non-deprived eye as dark regions, while the right activity map shows areas dominated by the deprived eye. The histogram quantifies proportions of cortex dominated by the deprived (D) and non-deprived (ND) eyes, respectively; they are almost equal. The animal depicted in (B) had a convergent squint induced in the non-deprived eye at the time the deprived eye was re-opened. It then had 1.5 months of discordant binocular vision. Again, the left activity map shows areas dominated by the non-deprived (strabismic) eye as dark regions, while the right activity map shows areas dominated by the deprived eye. The proportion of cortex dominated by the deprived (D) eye is clearly reduced compared with that dominated by the non-deprived (ND) eye.

Hence, modification of one synapse, or one group of synapses, in a particular direction — LTD, for example — need not be matched by an equal but opposite modification — LTP, say — in another synapse or group of synapses. Instead, the modification threshold will shift because of changes in the time-averaged postsynaptic activity. For example, binocularly deprived animals would have a much lower modification threshold than animals reared in a normal environment or monocularly deprived animals [57]. In support of this model, in cortical slices

obtained from dark-reared rats LTP is enhanced and LTD diminished compared to normal light-reared littermates [58].

BCM theory has also provided a potential explanation for experimental results that have not been easily reconcilable by 'competitive' models. For example, the greater shift in ocular dominance caused by monocular deprivation compared to monocular inactivation with tetrodotoxin can not be explained by 'competitive' models, but is predicted by BCM theory [59,60]. This experiment also demonstrated that homosynaptic LTD was necessary to induce the ocular dominance shift. Similarly, in the cat, simply restoring vision to the deprived eye following an early period of monocular deprivation results in good physiological and behavioural recovery [61–63]. 'Competition' between inputs from the two eyes should not allow recovery of vision in the deprived eye, as it would not have gained a competitive advantage. This finding led to the suggestion that absolute, rather than relative, levels of evoked activity in afferents representing the two eyes determine the degree of recovery from monocular deprivation [63].

Interestingly, the BCM model predicts recovery of the deprived eye only if inputs from the two eyes are temporally correlated [64]. We recently tested the role of correlated activity in the recovery of visual cortical responses and of visual acuity following a brief period of monocular deprivation imposed during the critical period [63]. Ten kittens had one eye closed for 10 days during the critical period. In five kittens, this eye was then simply re-opened and the animals were allowed to recover for at least 2 weeks. In the other five kittens, the non-deprived eye was made strabismic at the time of re-opening of the deprived eye, thereby decorrelating activity in the two sets of geniculocortical afferents. The kittens with concordant binocular vision displayed greater physiological recovery, both in the territory in V1 dominated by the previously deprived eye (Figure 3) and in the orientation selectivity of responses through that eye; they also attained a visual acuity in the deprived that was about twice as high as in the strabismic kittens.

We found that physiological recovery in the strabismic kittens was inversely related to the angle of squint, supporting the notion that the degree of correlated binocular input will predict the degree of recovery of synapses representing the deprived eye [65]. Our results may also explain why recovery of the deprived eye after simply re-opening it is very limited in monkeys [66]: given their much smaller receptive fields, the small angle of squint that often accompanies monocular deprivation [67,68] is likely to decorrelate inputs from the two eyes and preclude recovery.

According to an associative learning rule — an extension of homosynaptic learning [3] — the strengthening of deprived-eye synapses will depend on coincidence of pre-synaptic and post-synaptic activity, with the latter being determined largely by the activity pattern of inputs from the non-deprived eye. At the end of the deprivation period, any layer 4 neurons that were binocular prior to monocular deprivation will be dominated by the non-deprived eye. In animals with

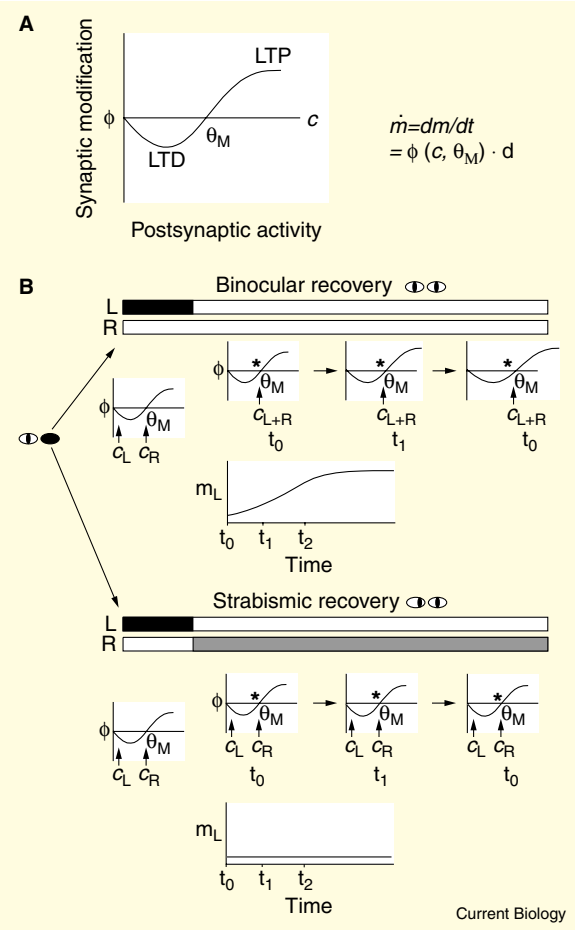


Figure 4. Dependence of recovery from monocular deprivation on correlated binocular input, as predicted by BCM theory.

(A) The model. The synaptic weight m of a particular synapse changes in time as a product of the presynaptic activity (d) and a non-linear modification function ($\phi$) of the postsynaptic activity ($c$) and the modification threshold ($\theta_M$). According to the BCM model, LTP occurs at a synapse when presynaptic activity is sufficient to cause depolarization of the postsynaptic cell above the modification threshold, while levels of depolarization below this threshold leads to LTD. (B) The predicted changes with time in the synaptic weights ($m_L$) of inputs representing the deprived (left) eye for recovery with or without concordant binocular vision. $c_L$ and $c_R$ represent the levels of postsynaptic activity due to stimulation of, respectively, the left (deprived) and right eye. In the situation of binocular recovery; $c_{L+R}$ represents the postsynaptic activity resulting from simultaneous stimulation of both eyes. As inputs from the two eyes are correlated, the postsynaptic activity caused by their sum is above the modification threshold $\theta_M$ set previously by the non-deprived eye. Because activity in the deprived-eye inputs are active when the postsynaptic activity is above $\theta_M$, they will be strengthened and $m_L$ increases from time $t_0$ to $t_2$. As the postsynaptic activity increases, so too does the modification threshold — its value at $t_0$ is marked by * — but at a slower rate as it depends on the time-average of the postsynaptic activity. In contrast, during strabismic recovery, the inputs from the previously deprived eye are not correlated with the non-deprived eye inputs and therefore do not summate. As the former are not active when the postsynaptic activity is above $\theta_M$, they are not potentiated. The original modification threshold — marked by * — does not change from time $t_0$ to $t_2$, as it remains determined solely by the input from the non-deprived eye.

concordant binocular vision, inputs from the non-deprived eye will serve as 'teachers' for the deprived-eye synapses. In terms of BCM theory, in animals with correlated binocular input, the postsynaptic (cortical) neurons are treated as one population when normal vision is restored at the end of the monocular deprivation period (Figure 4). Deprived-eye synapses will be potentiated almost immediately; later, the rate of potentiation will slow down, as the modification threshold will increase in line with increasing average postsynaptic activity. In contrast, the induction of a strabismus means that all neurons that are already completely dominated by one eye will remain so after re-opening of the deprived eye. Postsynaptic activity resulting from deprived-eye input will be too low to surpass the modification threshold, so no recovery will be observed.

BCM theory also accounts for results obtained from reverse lid suture. The model predicts that, following monocular deprivation, recovery should be initiated sooner if binocular vision is restored than if the animal undergoes reverse lid-suture. This is because, at the end of the monocular deprivation period, the modification threshold is still relatively high because of the non-deprived eye input. At the start of binocular recovery (as described above) deprived eye inputs will combine with non-deprived eye inputs, provided they are correlated, surpassing the modification threshold and initiating recovery immediately. At the start of reverse lid suture, the deprived eye inputs will not be able to reach the modification threshold because its synapses have been weakened and the non-deprived eye is now closed. Hence, there will be a delay in recovery of the non-deprived eye until the modification threshold resets to a much lower value.

We have recently demonstrated that there is a 24–48 hour delay in the initiation of recovery of the previously deprived eye during reverse lid suture compared to during binocular recovery [69]. These data are in good agreement with previous findings [70,71]. Binocular neurons are rarely observed during reverse lid suture; instead, the inputs from the deprived eye are weakened prior to the increase in strength of the non-deprived eye. Similarly, a retraction of deprived-eye arbours precedes the expansion of non-deprived arbours during monocular deprivation as well as during reverse occlusion, providing indirect evidence that synaptic weakening may precede synaptic strengthening [48,50]. By 'competitive' models, synaptic strengthening and synaptic weakening should occur in parallel, keeping total synaptic weight constant. Taken together, these studies demonstrate that non-competitive, associative mechanisms play a key role in the changes of receptive field properties initiated by altered visual experience.

It should be pointed out that homosynaptic and heterosynaptic mechanisms can only explain developmental plasticity as far as synaptic strengthening and weakening is concerned; they do not account for gain or loss of synapses and consequent structural changes such as expansion and retraction of terminals. Heterocellular mechanisms seem the only way to explain changes in the morphological features of geniculocortical afferents following altered visual experience [48,50,72].

Most of the concepts addressed in this review have been around for a long time, arising from seminal neurophysiological and anatomical studies in the 1960s and 1970s. In recent years, technical advances, for example in molecular biology or functional neuroimaging, have provided new tools to get answers to some of those questions. However, these new methods benefit from integration with more established approaches such as electrophysiological and behavioural studies as well as with neural modelling.

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